Review Article

PET-CT and PET-MR in urological cancers other than prostate cancer: An update on state of the art

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ABSTRACT

Hybrid positron emission tomography with computed tomography (PET/CT) and magnetic resonance imaging (PET/MRI) have enabled the combination of morphologic and functional imaging with the promise of providing better information in guiding therapy. Further advance has been made in the past decade with the development of newer radiotracers and optimization of the technical aspects. We performed a search in PubMed, Scopus, and Google Scholar for peer-reviewed literature concerning the advances and newer developments in the imaging of nonprostate urologic cancers between 2005 and 2017. This review aims at summarizing the current evidence on PET imaging in nonprostate urologic cancers and their impact on the diagnosis, staging, prognostication, response assessment, and restaging of these malignancies. However, much of the evidence is still in infancy and has not been incorporated into routine management or the practice guidelines of National Comprehensive Cancer Network or European Society for Medical Oncology (ESMO).

INTRODUCTION

Urological oncology is an active field in imaging research, and many modalities have been evaluated in the past few decades for the detection, characterization, and staging of urologic cancers. Metabolic imaging with PET has been evaluated for its ability to outperform conventional imaging modalities in urologic cancers. With the advent of hybrid positron emission tomography with computed tomography (PET/CT) and magnetic resonance imaging (PET/MRI), morphologic and functional imaging has been combined with the promise of providing better information in guiding therapy. This review aims at summarizing the current evidence on PET imaging in nonprostate urologic cancers and their impact on the diagnosis, staging, prognostication, response assessment, and restaging of these malignancies.

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RENAL CANCER

Contrast-enhanced CT (CECT) is the imaging modality of choice in the preoperative workup of patients with renal cell carcinoma (RCC). It provides information on the local extent, lymph node and vascular involvement, multifocality as well as distant metastasis. Any enhancing mass in the kidney is considered RCC and is seldom biopsied. Biopsy, at present, is limited to patients having extensive metastatic disease or significant comorbidities which preclude surgery, imaging features classical of triphasic angiomyolipoma, suspicious lymphoma, renal metastasis or infection, and in masses smaller than 3 cm where percutaneous or laparoscopic ablation may be considered.[1] CECT has limited value in differentiating benign from malignant masses or in the grading of tumor. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT plays an important role in the preoperative workup of patients with RCC. In a meta-analysis, Wang *et al*. noted that FDG PET had a pooled sensitivity and specificity of 62% and 88% for renal lesions and 79% and 90% for extrarenal

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lesions. The lower performance in detecting renal lesions has been hypothesized to be secondary to obscuration by urinary FDG activity.[2] Takahashi observed that based on the SUV values, PET/CT could differentiate high-grade from low-grade tumors with cutoff SUV_{max} of 3.0 having sensitivity and specificity of 89% and 87%, respectively.[3] Nakajima *et al*. found that higher FDG uptake correlated with higher Fuhrman grade, higher tumor, node, metastasis stage, and the presence of vascular and lymphatic invasion.[4] Similar results have been observed by multiple authors.[5-8]

In addition, it is sometimes possible to differentiate malignant renal tumors from benign etiologies. High-grade clear-cell RCC and papillary RCC had significantly higher SUV values than normal renal tissue whereas low-grade RCC and chromophobe RCC did not. SUV_{max} of 2.2 had sensitivity and specificity of 65% and 89% in differentiating benign and malignant tumors.[3] One study used dual tracer (^{11}C-acetate and ^{18}F-FDG) PET and observed that low-grade RCC, chromophobe RCC, and low-grade clear-cell RCC showed high uptake on ^{11}C-acetate PET and poor uptake with ^{18}F-FDG, whereas opposite results were obtained with papillary RCC and high-grade clear-cell RCC.[9] Schuster *et al*. noted that papillary RCC showed uptake with the leucine analog radiotracer ^{18}F-FACBC, unlike other RCC subtypes.[10]

PET/CT can detect metastasis in subcentimetric nodes, which are not considered significant on CECT.[11] PET/CT also can differentiate tumor thrombus from bland thrombus using cutoff SUV_{max} values.[12] It has a well-established role, better than CT in detecting and quantifying the metastatic burden in RCC, thereby having a significant impact on the management.[13-15] Even a single, doubtful metastatic lesion on CT can be evaluated with PET/CT.[16] There is a significant difference in the SUV_{max} of RCC with and without metastasis.[17] PET/CT is better than ^{99}Tc-MDP bone scan in evaluating bone metastasis as many of these lesions are osteolytic and missed on bone scan, whereas FDG uptake depends on metabolic rather than osteoblastic activity.[18] The ability of FDG PET to assess tumor grade and metastatic burden has enabled prediction of prognosis and survival in RCC.[19-21] Recently, multiple studies confirmed the usefulness of ^{68}Ga PSMA PET as well as the PSMA targeted ligand ^{18}F-DCFPyl in the staging of RCC.[22-24]

PET/CT has an important role in the active surveillance of patients after radical nephrectomy in detecting local or systemic recurrence.[25-27] Since PET/CT can evaluate all organ systems in one examination and does not require contrast, it could replace the conventional imaging modalities in restaging RCC.[11] In a large meta-analysis, Ma *et al*. demonstrated pooled sensitivity and specificity of 86% and 88% in the restaging of RCC.[14] False-negative cases are largely due to small size of the lesion and limited spatial resolution of the scanner. False-positive results occur due to concomitant infection, postoperative scar, or postradiation inflammation.[25,28] In a study of 104 patients with proven recurrence after surgery, Alongi *et al*. observed the sensitivity and specificity of FDG-PET to be 74% and 80%, respectively, with the PET findings having influenced the management in 43% of the patients. Positive PET was associated with worse survival rates over a period of 5 years.[28] Park *et al*. noted that the positivity on FDG-PET in recurrence was not influenced by the nuclear grade of the tumor.[29] Nakatani *et al*. observed that the sensitivity rose to 100% for recurrent papillary RCC as against other subtypes.[30]

Advanced, unresectable RCC is resistant to conventional chemotherapy and radiotherapy. Tyrosine kinase inhibitors (TKIs) such as sunitinib and sorafenib are effective in such cancers; however, the estimation of response assessment using mere size criteria might be fallacious with some even showing an early increase in size despite response. PET/CT might have a role in the early prediction of response and survival in such patients.[31-33] Kayani *et al*. observed that 57% of RCC cases treated with sunitinib showed FDG PET/CT response (defined as 20% reduction in SUV_{max}) at 4 weeks, but only the results at 16 weeks were prognostically significant.[34] Response with TKI was seen regardless of the site of metastasis and this did not have a bearing on the initiation of TKI.[35] Farnebo *et al*. observed that volumetric FDG-PET assessment using SUL_{peak} and total lesion glycolysis predicted progression-free survival (PFS) and overall survival (OS) as early as 14 days after initiation of therapy, whereas SUV_{max} did not.[36] Several other tracers have been used in assessing response to TKI.

Hugonnet *et al*. used ^{18}F-fluoromisonidazole (FMISO) PET, a marker of hypoxia, to assess response to TKI and observed that patients with initially hypoxic tumors had shorter PFS.[37] The uptake on ^{18}F-FMISO PET decreased 1 month after initiation of TKI and suggested response. Horn *et al*., in a study comparing ^{18}F-fluorothymidine (FLT) PET (a marker of cellular proliferation) and ^{18}F-FDG PET, observed that response was seen at an earlier time point with FLT-PET.[38] This suggested that TKI halted tumor proliferation earlier than glycolytic metabolism. Similarly, ^{18}F-fluoroethylcholine PET, ^{11}C-acetate PET, and ^{68}Ga-PSMA PET also have also been evaluated in response assessment in RCC.[39-41] The preliminary results of a study by Antunes *et al*. suggest that radiomics analysis on PET/MRI could be a powerful tool in evaluating response assessment of RCC.[42] Of late, carbonic anhydrase IX (CAIX) has been a topic of active investigation in RCC. Mutation of VHL leads to CAIX expression in most clear-cell RCCs. ImmunoPET with radiolabelled antibodies to CAIX has been observed in *ex vivo* and *in vivo* studies to identify clear-cell RCC lesions, act as a favorable prognostic biomarker and help guide radioimmunotherapy.[43] Clinical studies are in the infancy with one multicenter study

that used ^{124}I-girentuximab (cG250) PET having reported sensitivity and specificity of 86.2% and 85.9%.[44]

In summary, currently, there is not enough evidence to support the use of FDG-PET in the initial diagnosis or local staging of RCC. However, it is useful in the distant staging of RCC, restaging after surgery as well as in the assessment of response to chemotherapy. None of the guidelines from international policy-making bodies (European Society for Medical Oncology [ESMO] or National Comprehensive Cancer Network [NCCN]) support its routine use. The newer tracers hold promise, however, are experimental at present and require larger studies.

MALIGNANT ADRENAL TUMORS

The most common imaging modalities used to evaluate adrenal masses are CECT and MRI. Adrenal protocol in CT involves unenhanced imaging followed by venous phase (60–70s) and delayed phase (15 min) imaging. An unenhanced attenuation of less than 10HU, absolute and relative percentage washout more than 60% and 40%, respectively, are suggestive of adenoma. Similar is the case for a mass that shows significant loss of signal in opposed-phase images as compared to in-phase MR images. PET/CT also has been evaluated in adrenal mass evaluation. Several initial studies used quantitative parameters (SUV cutoff and adrenal to liver mean SUV ratio) in differentiating benign and malignant adrenal masses.[45,46] A large meta-analysis of 1391 lesions suggested that mere qualitative assessment of PET/CT had sensitivity and specificity of 97% and 91% in characterizing an adrenal mass as malignant. Qualitative analysis was found to be variable and not required in evaluating an adrenal mass but was considered helpful in assessing therapeutic response.[47] False-negative results were rare and benign lesions causing marked FDG avidity were extremely unusual.[48] However, false-positive cases were seen with few adenomas and infections, which showed mild FDG uptake (greater than the liver uptake) and the authors recommended caution while labeling these as outright benign or malignant.[47] Such lesions need to be assessed further with CT densitometry, contrast washout characteristics, MRI or follow-up imaging. Percutaneous biopsy must be resorted to if earlier characterization is required.[49] In another study, when both CECT and PET/CT criteria where used to characterize adrenal masses in oncologic patients, positivity in both increased the specificity for the diagnosis of metastasis to 91.2%, at the cost of decreased specificity (70.6%).[50] However, Brady *et al*. noted that combining unenhanced CT and SUV cutoff of 10 HU and 3.1, respectively, increased specificity by reducing the false-positive cases without sacrificing sensitivity.[51]

A multicenter retrospective study of malignant adrenal lesions showed that PET/CT had better accuracy than CECT in the diagnosing malignancy in case of adrenocortical carcinomas (ACC), lymphomas and neuroblastomas, and similar accuracy in case of malignant pheochromocytomas.[52] However, till date, PET/CT is not useful in differentiating the different malignant subtypes. In the workup of ACC, PET/CT is able to detect more distant metastasis than CECT.[53,54] PET/CT is also helpful in identifying metastasis which are occult on CT, as well as in accurately targeting biopsies in tumors with hemorrhage and necrosis, as well as in collision tumors.[55] In malignant pheochromocytomas, PET/CT was better than ^{131}I-MIBG SPECT/CT in identifying high-grade tumors, since the latter showed uptake only in well-differentiated tumors. PET/CT also was better at detecting metastasis.[56,57]

Takeuchi *et al*. showed that PET/CT and CECT fare similarly in the detection of primary and recurrent ACC; however, PET/CT could change the management in a small number of patients who were negative on CECT. PET/CT was also better than CECT in response assessment as decrease in tumor metabolism occurred before the reduction in size. However, no PET/CT parameters could predict survival at initial diagnosis or in recurrence.[58] Ardito found PET/CT to be less sensitive than CECT in detection of lung and liver recurrences of ACC; however, since PET/CT was more specific, it influenced the management in patients who were negative on PET/CT and positive on CECT.[59]

PELVIC AND URETERIC CANCERS

Evaluation of primary tumors of the pelviureteric system by FDG-PET is limited because of the normal urinary activity, especially in small tumors.[60] Despite this, Asai *et al*. observed a sensitivity of 83% for upper urinary tract urothelial cancers, with no correlation between the uptake and tumor stage/grade.[61] PET/CT is superior to CECT in the detection of distant metastasis and influenced the management in a significant number of patients.[62] One study observed better OS and PFS for patients who showed response on PET/CT after two cycles of first-line chemotherapy.[63] PET/CT is also more accurate than CECT for detecting local and distant recurrence postsurgery.[64]

BLADDER CANCER

PET evaluation of bladder cancers is limited by the urinary activity which obscures tumors and limits detection and locoregional staging. Cystoscopy is the gold standard in screening for bladder masses in patients who are positive on cytology. MRI is more sensitive to picking up bladder tumors than CECT or PET/CT. In a meta-analysis, Wang *et al*. showed a pooled sensitivity of 80% for FDG PET/CT in detecting bladed cancers.[65] Lodde at al observed PET/CT to be slightly more sensitive than CECT to the detection of bladder cancer (85% vs. 77%), but less specific (25% vs. 50%). For detection of nodal metastasis, PET/CT was more sensitive (57% vs. 33%) but

equally specific (100%).[66] Subsequently, several authors tried oral hydration and delayed imaging to increase detection rate.[67,68] Nayak *et al*. evaluated FDG PET/CT postforced diuresis with 20–40 mg of Furosemide, which improved conspicuity of the lesions with better sensitivity to detection of the primary tumor and pelvic lymph nodes than CECT (96% and 78% vs. 92% and 44%).[69] PET/CT has no role in prediction of muscle invasion in bladder cancer for which cystoscopy guided deep muscle biopsy remains the gold standard.

PET/CT has established role in metastatic workup of bladder cancer. Muscle-invasive bladder cancers require radical cystectomy, a morbid procedure. Detection of distant metastasis avoids surgery and can have therapeutic impact. A meta-analysis showed pooled sensitivity and specificity of 82% and 89% for PET/CT in detecting metastasis in primary and recurrent bladder tumors.[70] Mertens *et al*. noted that the better detection of metastasis altered the management in 20% of their patients with muscle-invasive tumors.[71] Similar observations were made by multiple other authors.[72-74] Another study observed that the presence of PET-avid extravesical lesions was associated with poor OS in patients with muscle-invasive cancers.[75] PET/CT has also been used in assessing response to neoadjuvant therapy.[76] PET responders on chemotherapy have been observed to have better survival.[63] PET/CT is also valuable in restaging bladder cancer postradical cystectomy, in detecting both local recurrence and distant metastasis.[77]

^{11}C-choline PET was introduced into bladder cancer imaging due to its little urinary excretion and was expected to be a promising tracer.[78,79] However, most subsequent studies failed to observe significant improvement over CECT or FDG PET/CT.[80,81] ^{11}C-methionine and ^{11}C-acetate PET/CT also have been evaluated and found to be better than FDG PET/CT in the detection of primary tumor and nodal metastasis. However, the evidence with these agents is insufficient to recommend routine usage.[82,83]

PET/MRI holds promise due to its superior soft-tissue resolution and increased the confidence with which metastatic lesions can be diagnosed. Usage of dynamic contrast enhanced as well as diffusion-weighted MRI can improve the detection of local tumor, nodal, and distant metastasis as well as prediction of muscle-invasion.[84,85]

In summary, FDG-PET is not useful in the local diagnosis or staging of bladder cancer. However, there is good evidence supporting its usefulness in the distant metastatic assessment of primary as well as recurrent cancer. Newer tracers are promising but lack sufficient evidence to support routine use. Neither NCCN nor ESMO guidelines support the routine use of PET in bladder cancer.

TESTICULAR TUMORS

Currently, CECT is used for staging and response assessment. Subcentimetric RP nodes are common in CECT of the abdomen. Detection of micrometastasis in subcentimetric lymph nodes is not possible on CECT, which relies on size and morphologic criteria. In addition, residual soft tissue is consistently visualized in the postchemotherapy CT of patients with complete response and has been attributed to fibrosis. CECT is limited in the differentiation of fibrosis and residual tumor. Hence, PET/CT has been extensively evaluated in the staging as well as restaging of testicular cancers. Ambrosini *et al*. observed PET/CT to have good sensitivity and specificity for detection of Seminoma lesions (92% and 84%, respectively), however, the sensitivity was lower for non-seminoma lesions (77%). PET/CT influenced the management in a significant number of patients for both the types. Tregalia *et al*. performed a large meta-analysis and observed PET/CT to have a pooled sensitivity and specificity of 78% and 86% in the assessment of postchemotherapy residual lesions. They noted PET/CT to have a high negative predictive value and the lesions missed are mostly subcentimetric. The authors recommend only follow-up for PET-negative lesions, even when they are larger than the CT cutoff size of 3 cm.[86] Similar results were observed by multiple other authors.[87-89] False-positive results were high, largely due to posttreatment inflammatory changes. Hence, an interval of 6 weeks should be kept between the end of chemotherapy and the PET/CT to reduce inflammatory changes.[86,87] Since mature teratomas do not show FDG uptake, PET/CT is not recommended in the response assessment of non-seminomatous tumors.[90]

PET has validated role in the follow-up of seminomatous germ cell tumors. As per the ESMO and NCCN guidelines, FDG-PET is recommended 6 weeks' postchemotherapy for residual masses larger than 3 cm. For smaller masses, PET may be performed however, the positive predictive value is lower and surveillance is preferred. PET is not recommended in the initial staging of testicular tumors or the follow-up of nonseminomatous tumors.

PENILE CANCER

The role of PET/CT in the evaluation of penile cancer is ambiguous. Almost all cancers show uptake on PET; however, PET/CT is not recommended for primary tumor staging. Multiple studies have used PET/CT in the detection of micrometastasis in clinically N0 disease (non-palpable nodes) and found variable, but generally low sensitivity.[91-93] One meta-analysis showed pooled sensitivity of only 57%, which makes surgical staging necessary despite its morbidity. The same study observed a pooled sensitivity of 96% for clinically palpable nodes.[94] For pelvic lymph node as well as distant metastatic assessment, PET/CT is extremely

Table 1: Summary of the currently available radiotracers, their functions, potential applications, and European Society for Medical Oncology/National Comprehensive Cancer Network practice recommendations in urologic cancers

Cancer	Tracer	Function	Potential applications	Recommendations (ESMO/NCCN)
Renal cancer	^{18}F-FDG	Glucose analog	Metastatic work up, restaging, treatment response	None
	^{11}C-acetate	Fatty acid oxidation	Diagnosis, staging, treatment response	
	^{68}Ga-PSMA	Membrane antigen	Metastatic workup, treatment response	
	^{18}F-FMISO	Indicates hypoxia	Treatment response	
	^{18}F-FLT	Thymidine analog	Treatment response	
	^{18}F-choline	Membrane synthesis	Treatment response	
	^{124}I-cG250	Antibody to CAIX	Diagnosis, prognostication	
Bladder cancer	^{18}F-FDG	Glucose analog	Metastatic workup, restaging	None
	^{11}C-acetate	Fatty acid oxidation	Diagnosis, nodal staging	
	^{11}C-choline	Membrane synthesis	Diagnosis, nodal staging	
	^{11}C-methionine	Amino acid turnover	Diagnosis, nodal staging	
Testicular cancer	^{18}F-FDG	Glucose analog	Nodal and distant metastatic workup, follow-up in seminomatous tumors	Follow-up of seminomatous tumors after chemotherapy (residual tumors larger than 3cm)
Penile cancer	^{18}F-FDG	Glucose analog	Nodal and distant metastatic workup in patients with palpable inguinal nodes	None

NCCN=National Comprehensive Cancer Network, ESMO=European Society for Medical Oncology, ^{18}F-FDG=Fluorine-^{18}-Fluorodeoxyglucose, ^{18}F-FMISO=^{18}F-fluoromisonidazole, ^{18}F-FLT=^{18}F-fluorothymidine, CAIX=Carbonic anhydrase IX

useful and more accurate than CECT. The performance is better if palpably enlarged inguinal lymph nodes are present.[95] However, the evidence is insufficient and is not recommended by NCCN or ESMO as of now.

CONCLUSION

Metabolic imaging with FDG PET is limited in urologic cancers because of the high urinary activity of the radiotracer. Metabolic imaging with PET/CT and PET/MRI is advancing with newer tracers being discovered and tested. The need to optimize technical factors in hybrid PET/MRI for the best results is also a challenge to be dealt with. Combining the metabolic data of PET with MRI holds great promise; however, sufficient evidence supporting its routine use is not available at present except in the follow-up of seminomatous germ cell tumors of the testis. A summary of the potential applications of FDG-PET, newer tracers, and the current ESMO/NCCN guidelines are provided in Table 1.

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